CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-555/S-003/S-004

MEDICAL REVIEW

L. TALAMO
180

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	20-555 Suppl. No. S-003
Date Submitted:	December 16, 1996
Sponsor:	Whitehall-Robins Healthcare Madison, N.J.
Name of Product:	AXID® AR (nizatidine)
Formulation:	Tablets (75 mg)
Route of Administration:	Oral
Pharmacological Category:	H_2-receptor antagonist (anti-ulcer; anti-GERD)
Indication Sought:	New indication: Treatment of heartburn, acid indigestion, and sour stomach
Material Reviewed:	Results from two identical, multi-center, multiple-dose, randomized, parallel-group, 2-week (with a 1 week single-blind antacid qualifying period) pivotal trials submitted in support of the indication sought.
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.

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I. BACKGROUND INFORMATION

The drug which is the subject of this application is AXID® AR. The approved USAN generic name of the compound is nizatidine (=NIZ).

NIZ is a competitive, reversible inhibitor of histamine at the histamine H_2-receptors, particularly those in the gastric parietal cells. NIZ is currently marketed for oral administration in the United States as AXID® capsules, by Eli Lilly and Company (NDA 19-508). The currently approved indications for oral NIZ include 1) short-term (up to 8 weeks) Tx of active DU (300 mg once daily at bedtime; an alternative dosage regimen is 150 mg once daily at bedtime); 2) maintenance (up to 1 year) of healed DU (150 mg once daily at bedtime); 3) short-term (up to 12 weeks) treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn (HB) due to GERD (150 mg twice daily).

AXID® AR (nizatidine) non-prescription tablets, 75 mg, is currently approved for non-prescription use for the prevention of meal-induced heartburn when taken 30 to 60 min. prior to a provocative meal.

This application provides for a new indication for the treatment of heartburn, acid indigestion, and sour stomach. In support of this indication, the sponsor has submitted results from two identical pivotal, multi-center, multiple-dose, placebo-controlled, randomized, parallel group, 2-week (with a 1 week single blind antacid qualifying period) clinical efficacy and safety studies [NZ-95-01 and NZ-95-04] and a non-pivotal study [WM-505]. This application consists of 70 volumes.

II. CLINICAL CONDITION TO BE TREATED

A. Generalities

HB or pyrosis usually is described as a substernal pain or burning sensation that typically radiates orad, to the entire retrosternal area, the neck, occasionally to the back, and rarely into the arms. HB is often accompanied by a sour or bitter taste in the mouth. On occasion, actual regurgitation of gastric contents also occurs.

HB is probably the most common GI complaint in the Western population. A 1988 Gallup Survey and another survey [O. Nebel et al., Dig. Dis. Sci. 21:953 (1976)] of American subjects revealed that 33 to 44% complain of HB at least monthly and 7 to 13% may have daily symptoms[1]. HB reaches its maximum frequency during pregnancy when, according to Nebel et al. [(locus cited) (1976)], 25% of patients may be found to have daily symptoms. Most people do not consider HB a medical problem and seldom report this to their physicians (Gallup Survey on HB (1988)].

[1] Likewise, interviews with healthy Britons found that 33% had experienced HB, with 10% having monthly symptoms and 3%, daily symptoms [W.A. Thompson and K.W. Heaton, Can. Med. Assoc. J. 126:46 (1982)].

B. Mechanisms Responsible for the Symptoms of HB

The mechanism(s) responsible for the symptom of HB is(are) far from clear[2]. What is known is that HB is predictably aggravated by multiple factors, and that this aggravation may work through at least three mechanisms.

a. Low LES Pressure

[J.E. Richter and D.O. Castell, Med. Clin. No. Amer. 65:1223 (1981)]
Certain foods: fats, sugars, chocolate, onions, carminatives, coffee

Alcohol, Cigarettes

Medications: progesterone, theophylline, anticholinergic agents, β-adrenergic agonists, α-adrenergic antagonists, diazepam, meperidine, nitrates, Ca channel blockers.

b. Direct Mucosal Irritant

Certain foods: citrus products, tomato-based products, spicy foods, coffee

Medications: Aspirin, NSAIDs, tetracycline, quinidine, KCl tablets, iron salts

c. Increased Intraabdominal Pressure[3]

Maneuvers such as bending over, lifting heavy objects, straining at stool, performing isometric exercise.

d. Other

- Supine position, red wine, emotions.
- HB may occur with or without hiatal hernia.

Patients with HB seek relief with OTC antacids, which have been approved, by OTC monograph, for the relief of heartburn, sour stomach, and or acid indigestion and upset stomach associated with these symptoms. The effectiveness of the antacids for these indications is thought to be related to their ability to neutralize acid. The sponsor of this NDA proposes that, by virtue of its ability to inhibit gastric acid secretion, NIZ also should be effective in the treatment of HB and the above-described related symptoms.

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[2] According to one proposal [F. Ismail-Beigi et al., Gastroenterology 58:163-174 (1970); L.F. Johnson et al., Amer. J. Dig. Dis. 213:498-509 (1978)], chronic exposure of the esophageal epithelium to noxious gastric juices may cause neural sensory receptors normally located in the deeper layers of the esophageal epithelium to become more superficial in location. Prolonged acid exposure also increases the permeability of the esophageal epithelium to hydrogen and other ions [B. Khamis et al., Gut 19:396-398 (1978)]. The combination of these events may stimulate afferent nerve e...ings, thereby causing the sensation of HB.

[3] These factors do not affect LES pressure but are direct irritants to the inflamed esophageal mucosa [[S.F. Price et al., Gastroenterology 75:240 (1978)]. This mechanism is independent of pH and probably related to high osmolarity [D.A. Lloyd and I.T. Borda, Gastroenterology 80:740 (1988)].

It is also important to note that HB is the most typical symptom of GERD and that other g.i. disorders, such as PUD, gastritis, and duodentis may present with similar symptoms. In addition, HB may be confused with the substernal chest pain of angina, biliary colic, and primary esophageal motor disorders such as diffuse esophageal spasm and the nutcracker esophagus. According to the textbooks of Gastroenterology, in patients with typical symptoms of HB, no diagnostic evaluation is usually necessary. However, investigation is clearly indicated for patients with severe or unexplained symptoms, or dysphagia, and for those patients who fail to respond to standard medical therapy.

A simple way to demonstrate that a patient's symptoms are related to an acid-sensitive esophagus is the acid-infusion, or Bernstein's test. The procedure begins with control period of saline infusion. During this test, 0.1 N HCl is infused into the distal esophagus for 20 to 30 min. at a rate of 100 to 120 drops per min. Reproduction of the patient's burning substernal pain correlates well with the presence of endoscopic esophagitis [L.M. Bernstein and L.A. Baker, Gastroenterology 34:760-781 (1958)], although symptoms may be present without endoscopic findings.

A wide variety of other tests are available that may demonstrate the presence of reflux, damage caused by reflux and relationship of reflux to symptoms. In a study of patients with weekly HB symptoms seen in an outpatient setting, 12% were found on endoscopy to have changes of Barrett's esophagus [C. Winters et al., Gastroenterology 92:118-124 (1987)]. Barrett's esophagus is a known complication of chronic GER and has also been recognized to have an association with adenocarcinoma of the esophagus [S.J. Spechler and R.K. Goyal, New Engl. J. Med. 316:362-371 (1986)]. The implication of this finding in the evaluation of the patient with HB is uncertain at this time, although routine endoscopy cannot yet be justified for the evaluation of all HB patients.

III. PROPOSED LABELING CHANGES FOR AXID® AR

NOTE: Only additions or proposed modifications of the Approved labeling are listed below. Sections where no changes are being proposed are not listed.

PROPOSED LABELING FOR AXID® AR	INTEGRATED SUMMARY Volume/Page	STUDY REPORT Volume/Page
FRONT		
USES: • For Relief of heartburn, acid indigestion and sour stomach	ISE: 1.30/08-10861-8	NZ-95-01: 1.3/08-00127-41 NZ-95-04: 1.17/08-5414-28
• For Prevention of these symptoms brought on by consuming food and beverages.	Slight modification of approved labeling	Slight modification of approved labeling
DIRECTIONS: • For Relief of symptoms, take 1 tablet with water	ISE: 1/30/08-10855	NZ-95-01: 1.3/08-00083-4 NZ-95-04: 1.17/08-05369-70
• For Prevention of symptoms, take 1 tablet with water [redacted] food and beverages that cause you heartburn	Slight modification of approved labeling	Slight modification of approved labeling
Tips for managing heartburn • Avoid lying down flat or bending over soon after eating • Avoid eating late at night, or just before bedtime	Approved Labeling Slight modification of approved labeling	Approved Labeling Slight modification of approved labeling
BACK		
AXID AR contains an ingredient, nizatidine, that doctors have prescribed millions of times and has been taken safely with many frequently prescribed medications	ISS: 1.30/08-10939-40	Worldwide Safety: 1/30/08-10785-7 Item 2.C.: 1.3/02-00007
AXID AR works by reducing the production of stomach acid that can cause heartburn	Slight modification of approved labeling	Slight modification of approved labeling
In clinical studies, AXID AR was significantly better than placebo in completely relieving and preventing heartburn symptoms	(Relief) ISE: 1.30/08-10861-8 (Prevention) ISE: NDA 20-555, 1.69/08-019893-908	NZ-95-01: 1.3/08-00127-41 NZ-95-04: 1/17/08-05414-28
When taken as directed, AXID AR relieves and/or prevents heartburn from occurring	(Relief) ISE: 1.30/08-10861-8 (Prevention): Slight modification of approved labeling	(Relief) NZ-95-01: 1.3/08-00127-41 NZ-95-04: 1.117/08-05414-28
RELIEF **Benefit of AXID AR Compared to Placebo** **Combined Studies C and D** **Pills taken after symptoms occur**	ISE: 1.30/08-10855	NZ-95-01: 1.3/08-00083-4 NZ-95-04: 1.17/08-05469-70
(GRAPH) Percent of heartburn episodes completely relieved	ISE: 1.30/08-10867; 08-10893	NZ-95-01: 1.3/08-00136-7 [redacted]
(GRAPH) Percent of *more severe* heartburn episodes completely relieved	ISE: 1.3/08-10870-1; 08-10915	NZ-95-01: 1.3/08-00141 [redacted]
(GRAPH) Percent of subjects with complete relief at all episodes	ISE: 1/30/08-10867; 08-10874; 08-10895	NZ-95-01: 1.3/08-00139-40 [redacted]

IV. SPONSOR'S OVERALL APPROACH

The Clinical Development Program for OTC NIZ included studies previously performed a) as part of the clinical development of the prescription drug (no new standard studies were conducted but results of key PK/PD studies are referred to here for completion) and b) 3 pivotal and 3 supportive trials to assess the efficacy and safety of three dose levels of NIZ, compared to PL, in the prevention and reduction of post-meal HB symptoms. In the present submission, results of three clinical trials are presented. These three studies included two identical pivotal efficacy and safety studies (NZ-95-01 and NZ-95-04) and a nonpivotal trial (WM-505). The two pivotal trials evaluated the efficacy of NIZ 75 mg vs placebo in the treatment of HB at 15, 30 and 45 min. and 1, 2 and 3h after taking study medication. The non-pivotal trial evaluated the efficacy of NIZ 75 mg, antacid (magnesium hydroxide/ aluminum hydroxide), and placebo in the alleviation of HB. The main features of the design of these three trials and their adequacy in support of this application are summarized in VI., A., following the Summary of Clinical Pharmacology Section (V.).

V. SUMMARY OF CLINICAL PHARMACOLOGY

A. Generalities

In their submission in support of the prevention of HB OTC indication, the sponsor presented a short summary of the 31 Clinical Pharmacology studies from NIZ in NDA 19-508. Pertinent information was included in the labeling for the approved drug. Salient points are reproduced below.

Antisecretory Activity-1. Effects on Acid Secretion: Axid significantly inhibited nocturnal gastric acid secretion for up to 12 h. Axid also significantly inhibited gastric acid secretion stimulated by food, caffeine, betazole, and pentagastrin:

	Time After Dose (h)	% Inhibition of Gastric Acid Output by Dose (mg)				
		20-50	75	100	150	300
Nocturnal	Up to 10	57		73		90
Betazole	Up to 3		93		100	99
Pentagastrin	Up to 6		25		64	67
Meal	Up to 4	41	64		98	97
Caffeine	Up to 3		73		85	96

2. Effects on Other Gastrointestinal Secretions-Pepsin:

Oral administration of 75 to 300 mg of Axid did not affect pepsin activity in gastric secretions. Total pepsin output was reduced in proportion to the reduced volume of gastric secretions.

Intrinsic factor: Oral administration of 75 to 300 mg of Axid increased betazole-stimulated secretion of intrinsic factor.

Serum Gastrin: Axid had no effect on basal serum gastrin. No rebound of gastrin secretion was observed when food was ingested 12 h after administration of Axid.

3. Other Pharmacologic Actions--

a. Hormones: Axid was not shown to affect the serum concentrations of gonadotropins, prolactin, GH, ADH, cortisol, triiodothyronine, thyroxin, testosterone, 5α-dihydrotestosterone, androstenedione, or estradiol.

b. Axid had no demonstrable antiandrogenic action.

4. Pharmacokinetics-The absolute oral bioavailability of NIZ exceeds 70%. Peak plasma concentrations ([redacted] for a 150-mg dose and [redacted] for a 300-mg dose) occur from 0.5 to 3 h following the dose. A concentration of 1,000 μg/L is equivalent to [redacted] a dose of 300 mg is equivalent to [redacted] Plasma concentrations 12 h after administration are less than [redacted] The elimination half-life is 1 to 2 h, plasma clearance is 40 to 60 L/h, and the volume of distribution is 0.8 to 1.5 L/Kg. Because of the short half-life and rapid clearance of NIZ, accumulation of the drug would not be expected to individuals with normal renal function who take either 300 mg once daily at bedtime or 150 mg twice daily. Axid exhibits dose proportionally over the recommended dose range.

The oral bioavailability of NIZ is unaffected by concomitant ingestion of propantheline. Antacids consisting of aluminum and magnesium hydroxides with simethicone decrease the absorption of NIZ by about 10%. With food, the AUC and C_{max} increase by ca. 10%. In humans, <7% of an oral dose is metabolized as N2-monodesmethyl-NIZ, an H_2-receptor antagonist, which is the principal metabolite excreted in the urine. Other likely metabolites are the N2-oxide (less than 5% of the dose) and the S-oxide (less than 6% of the dose).

More than 90% of an oral dose of NIZ is excreted in the urine within 12 h. About 60% of an oral dose is excreted as unchanged drug. Renal clearance is about 500 mL/min, which indicates excretion by active tubular secretion. Less than 6% of an administered dose is eliminated in the feces. Moderate to severe renal impairment significantly prolongs the half-life and decreases the clearance of NIZ. In individuals who are functionally anephric, the half-life is 3.5 to 11 h, and the plasma clearance is 7 to 14 L/h. To avoid accumulation of the drug in individuals with clinically significant renal impairment, the amount and/or frequency of doses of Axid should be reduced in proportion to the severity of dysfunction.

Ca. 35% of NIZ is bound to plasma protein, mainly to α_1-acid glycoprotein. Warfarin, diazepam, acetaminophen, propantheline, [redacted] and propranolol did not affect plasma protein binding of NIZ in vitro.

B. PK/PD Studies Previously Submitted in Support of the Prevention of HB OTC Indication.

Included among these were the following studies.

1. Study WM-550 [n=12]

PK/PD Dose-Response of oral NIZ on Gastric Acidity in HB Sufferers

[redacted]

2. Study WM-575 [n=12]

The PDs of NIZ: Effect of Pre-Meal Dosing on Food-Stimulated Gastric pH in HB Sufferers

[redacted]

3. Study WM-578 [n=24]

A Placebo-Controlled, Dose-Ranging Study of the Effects of Nizatidine on the Prevention and Reduction of Reflux-Documented, Meal-Induced Heartburn

[redacted]

4. Study WM-529 [n=24 HV]

Relative Bioavailability of Nizatidine 75 mg, with and Without Antacid, in the Fed and Fasting States

[redacted]

5. Study B5O-LC-NBBP [n=16]

Nizatidine/Ethanol Interaction Study

The MO's Overall Summary/Conclusions on Clinical Pharmacology (MOR of June 22, 1995) are as follows.

- Reference is made to the antisecretory activity of NIZ at the oral dose of 75 mg, the proposed dose for OTC marketing. According to the information in the labeling this dose is less effective than 150 mg NIZ in the inhibition of GAO induced by betazole, pentagastrin, meal or caffeine. Depending upon the stimulus, the duration of effect for diurnal inhibition of GAO was 3 to 6 h. No data are cited for nocturnal GAO for the 75 mg NIZ dose. Except for nocturnal GAO (73% inhibition for up to 10h), there are no data evaluating the antisecretory effect of 100 mg NIZ but this dose produced a 73% inhibition of nocturnal GAO, lasting up to 10 h after dosing.

  According to these labeling data, single doses of NIZ of 20 to 50 mg inhibited meal-stimulated GAO by 41% but this percent inhibition was lower than that with 75 mg NIZ (64% of meal stimulated diurnal GAO), an effect that lasted up to 4 h.

- The results from the additional studies have provided additional information on the effects of 75 mg NIZ in comparison with 25 mg and 225 mg. These new studies did not test the effects of 50 mg NIZ. There are no strong reasons to propose the use of 25 mg ~~NIZ~~ (instead of 75 mg of the drug) but there is little information about the antisecretory effect of the 50 mg dose of the drug.

- In these pharmacology trials the parameters of evaluation included the duration of time that each dose elevated gastric pH >3 and >4, the time of onset of PD activity and the PK onset and duration of adequate NIZ concentrations >EC_{50} level (182 ng/ml) required to inhibit meal-stimulated gastric acid production. One parameter of interest was activity during the first 4h post-dosing.

- The results of Study WM-550 showed a dose-response trend in serum NIZ concentrations and derived PK parameters for the NIZ 225 mg, 75 mg and 25 mg doses evaluated. The AUEC for the NIZ 25 mg dose was

statistically significantly lower than for the 75 mg and the 225 mg doses. The three dose levels tested showed a dose-response effect on gastric pH levels over time and the derived PD parameters. Both the 75 mg and the 225 mg dose of NIZ produced a sustained gastric pH ≥4 for a clinically relevant time duration (>3h). The 25 mg dose of NIZ did not produce an adequate pH elevation or sustained it for the clinically relevant 3-h time period.

- Study WM-575 demonstrated a dose-response effect for NIZ doses of 75, 225 or 25 mg taken one hour prior to a meal. This conclusion was based upon the serum NIZ concentrations measured over time and the derived PK parameters. Also shown was a dose-response effect on post-meal gastric pH levels over time and in the derived PD parameters. In comparison to PL, both NIZ doses, 75 and 225 mg, produced significantly longer durations of pH ≥3 and ≥4. But the durations produced by the NIZ 25 mg dose were not statistically different from those of PL. Although all three NIZ doses resulted in a statistically significantly higher maximum pH than PL, the onset times for the NIZ 25 mg dose were comparable to PL and those for the higher doses were numerically but not statistically shorter than for PL.

- Study WM-578 showed a consistent dose-response effect for all three doses of NIZ on the measured parameters of gastric pH. Meal-related HB was reduced by both the 225 mg and the 75 mg NIZ in comparison to PL but the 25 mg was less effective and not differentiated from PL.

- The results of Study WM-529 showed no statistically significant between-Tx differences for serum and urine PK parameters, and this is taken as evidence that coadministration antacid [redacted] had no significant effect on NIZ (75 mg) absorption, bioavailability, or excretion. This lack of effect was shown in both the fasted and the fed states. Although food delayed the onset of NIZ absorption [redacted] the presence of food in the g.i. tract did not affect NIZ bioavailability or excretion.

- Study B5Q-LC-NBBP explored possible interactions between NIZ and alcohol. In patients given 0.15 or 0.45 g/Kg ethanol, Pre-Tx with a single (high) 300 mg dose of NIZ in fed individuals produced statistically significant increases in blood alcohol concentrations. The increases were small in magnitude and in these NIZ-Tx patients, blood alcohol concentrations did not go from below to above the legal limit (100 mg/dl) for driving under the influence. The reviewer agreed with the sponsor's conclusion that these changes in blood alcohol concentrations were neither clinically nor socially (legally) meaningful.

VI. MAIN FEATURES OF THE DESIGN AND ADEQUACY OF CLINICAL TRIALS IN NDA 20-555/SE1-003 (TABLE 1)

As summarized in this Table, both pivotal trials, NZ-95-01 and -04 were well-designed and well-controlled and are useful to demonstrate efficacy and safety of the proposed dose of NIZ (75 mg) for the treatment of HB. On the other hand, the non-pivotal trial WM-505 is of limited utility for the reasons enumerated under the Comments section of Table 1.

TABLE 1

Main Features of the Design and Execution and Adequacy of the Pivotal Trials
Submitted in Support of the Approval of NIZ 75 mg for the Treatment of HB

Study I.D.	Study Population/ Design	Summary of Execution	Groups Being Compared	COMMENTS
NZ-95-01 Total n=537 23 Investigators NZ-95-04 Total n=457 24 Investigators	M&W 16 to 81y of age with at least a 3-month history of HB responsive to antacids or nonprescription histamine H_2-receptor antagonists. Multi-center, multiple dose, PL-controlled, randomized, balanced parallel group study with 1-week S-B antacid qualifying period and 2-week DB treatment period.	• During the 2-week D-B treatment period, subjects treated up to two episodes of HB of at least moderate severity per day with NIZ 75 mg or PL. • Each episode was evaluated over 3h at 15, 30, 45 min., 1, 2 and 3h after dosing. • Subjects who had insufficient relief were permitted to take rescue medication after the 2-h post-dose assessment. • A 4-h interval from the start of study medication and resolution of the previous episode were required before treating a second episode on any one day of the study. • Completeness of HB relief was also assessed at the 3-h timepoint. • AEs were recorded at the end of the S-B and D-B treatment periods. • A subject's response profile comprised two components: 1) whether sustained adequate relief was attained, and 2) the rapidity with which it was attained. For any individual episode of HB, the Sustained Adequate Relief Score (SARS), a categorical score of 0 to 4, was assigned based on the time taken to achieve sustained adequate relief for that particular episode. The primary unit of statistical analysis was the subject and efficacy was based on the average score across the first four episodes to provide an analysis of whether sustained adequate relief of HB was attained more frequently and/or sooner in the NIZ-treated group than in the placebo-treated group.	NIZ 75 mg n=272 vs PL n=265 Up to two doses per day NIZ 75 mg n=226 vs PL n=231 Up to two doses per day	• Both of these pivotal trials are adequate and well-controlled. • The primary endpoint (SARS) of efficacy is adequate. • Efficacy is demonstrated by showing superiority of the NIZ 75 mg over PL in the relief (more frequently and/or sooner) of HB.

WM-505 Total n=95 4 Investigators	M&W 19 to 79 y of age with at least 6 HB episodes per week of mild or greater severity to qualify at screening and at least 12 episodes during the 2-week S-B antacid qualifying period. Multicenter, multiple dose, PL-controlled, randomized, balanced parallel group study with a 2-week S-B antacid qualifying period, and a 2-week D-B treatment period.	• The primary efficacy variable was the proportion of episodes for which at least moderate "relief" was achieved by 60 min. • Subjects were permitted to use up to twice as much NIZ per day and remedicate after 1h for any single episode.	NIZ 75 mg n=31 vs P L n=32 vs ANTACID n=32 Up to 4 doses per day	• Study of limited utility. • Study considered non-pivotal for reasons that include: 1) small number of patients 2) different study population that was required to have a Hx of at least 6 episodes per week of mild or greater severity to qualify at screening. 3) The frequency of at least 12 episodes during the 2-week S-B antacid qualifying period was higher than the frequency of 3 episodes per week required for the pivotal studies (see above). 4) The minimum severity of episodes required (mild) was less than that required for the pivotal trials (moderate). 5) Subjects were permitted to use up to twice as much NIZ per day and remedicate after 1h for any single episode. 6) The primary efficacy variable, the proportion of episodes for which at least "moderate" relief was achieved by 60 min., differed from that of the pivotal trials (mean SARS for the first 4 episodes).

VII. STUDY NZ-95-01

RELIEF OF EPISODIC HEARTBURN: SAFETY AND EFFICACY OF NIZATIDINE 75 MG - A PLACEBO CONTROLLED STUDY"

The study dates were March 1996 - August 1996 and the report date November 1996. The study was carried out in accordance with GCP [redacted]

1. Objective

According to the protocol, this study was set to demonstrate the comparative safety and efficacy of oral NIZ 75 mg, taken as needed up to twice daily vs PL in episodic HB relief.

2. Study Design

From all the information given in the Clinical Report, Appendices, Tables and related materials this 23-Investigator trial was well-designed (multicenter, randomized, double-blind, PL-controlled balanced-parallel-group approach lasting three weeks). A 1 week single-blind antacid response qualifying period was followed by a 2-week double-blind treatment period.

3. Study Population

As summarized in Table 2, the study population was adequate for this type of study. The clinical investigations were conducted as "at home" studies to evaluate efficacy of the drug in the same environment where consumers would be treating their HB with NIZ 75 mg when it will be indicated for nonprescription use for the relief of episodic HB.

TABLE 2
Study NZ-95-01

Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
Single-blind Antacid Qualifying Period • 16y of age or older, with a minimum 3-month Hx of HB defined as a substernal burning discomfort radiating cephalad, that is experienced a minimum of 3 times/week and is of moderate or greater severity. Moderate HB is defined in the protocol as HB that bothers the subject but does not interfere with daily activities. • Hx of use of OTC antacid and/or OTC histamine H_2-receptor antagonists for the treatment of HB. • General good health, documented by the Investigator's Hx and P.E. • Willingness to participate in the study in accordance with the requirements of the protocol, e.g., agreement not to treat HB with anything but blinded test medication or the supplemental antacid provided by the sponsor. • Written IC for those legally able to give consent. Double-blind Treatment Period Meets all of above criteria and shows: • Documented ability to follow study procedures and fill out diaries. • Record of at least three HB episodes in the S-B period, rated as moderate or greater severity, with at least 50% of such episodes adequately relieved by S-B antacid or rescue medication at any time during the 3-h assessment period.	• Hx of esophageal or gastric surgery other than surgery for infantile pyloric stenosis. • Hx of upper GI or esophageal Dz other than hiatal hernia. Examples of exclusions are: PU, pyloric stenosis, GI malignancy, esophageal stricture, esophageal ring, esophageal bleeding, symptoms of dysphagia, unexplained weight loss or melena. • Concurrent other GI or systemic illness that would, in the opinion of the Investigator and medical monitor, preclude the use of NIZ or confound the evaluation of efficacy. • Any concurrent serious systemic disorders, such as angina pectoris, uncontrolled HT, cardiopulmonary, renal or hepatic insufficiency, PA or uncontrolled DM. • Hx of (within the past 2y) or current abuse of alcohol or drug substances. • Current treatment with a regular, multiple-times a day regimen of ASA or NSAIDs. The use of a once daily or every other day regimen of ASA for platelet inhibition and the use of occasional ASA or NSAIDs for conditions such as headache were allowed provided the time restrictions of the protocol were followed. • Use of PPI or investigational agent within the past 30 d. • Use of prokinetic or anticholinergic agent, sucralfate or histamine H_2-receptor antagonist within 7 days. • Hx of hypersensitivity, significant adverse experience, or contraindication to any H_2 or antacid. • Pregnancy or lactation, or reliance on inadequate contraception (inadequate contraception was defined as abstinence alone, rhythm method alone, withdrawal alone, or partner's vasectomy alone). • Previous participation in this study or any other ongoing NIZ study. • Member of or related to a member of the study site staff directly involved with the study or to the sponsor.

4. Materials/Randomization/Blinding/Labeling/Storage and Accountability/Concomitant Medications

The clinical supplies were as follows:

Study NZ-95-01: Test Medication

Period	Study Drug	Per Tablet	Per Dose	Lot Number
Single-Blind	Single-blind Antacid[a]	480 mg (13.5 mEq)	480 mg (13.5 mEq)	WH-678-001A WH-678-001B
	Rescue Medication[b]	500 mg (10.3 mEq)	500 mg (10.3 mEq)	WH-464-009A WH-464-009B
Double-Blind	Nizatidine	75 mg	75 mg	WH-463-13W
	Placebo	Inert Ingredients	Inert Ingredients	WH-463-15D
	Rescue Medication[b]	500 mg (10.3 mEq)	500 mg (10.3 mEq)	WH-464-009A WH-464-009B
Both periods: interim episodes of heartburn	Supplemental Antacid[c]	500 mg (10.3 mEq)	500 mg (10.3 mEq)	WH-0692-001A WH-0692-001B

[redacted]
b) Tums® repackaged on medication cards
c) Tums® provided in commercial packaging

5. Clinical Procedures/Observations

There were three specified visits:

a. Visit 1
(Screening/Single-Blind Period)

At Visit 1, the Investigator of his/her designee examined each subject to determine his/her eligibility and entered the pertinent medical history information and clinical findings in the appropriate sections of the case report form. All subjects screened for possible inclusion in the study were recorded on the screening record form. Specific reasons for not including a subject in the study were provided. A checklist of the inclusion/exclusion criteria was completed during the pre-study screening period to determine subject eligibility. Women of child-bearing potential had to have a negative urine pregnancy test before study medication could be dispensed.

Subjects who satisfied all inclusion/exclusion criteria were enrolled in the single-blind antacid qualifying period of the study. The study coordinator supplied each subject with seven single-blind blister-pack medication cards and diaries sufficient for treating and evaluating up to two episodes per day for seven days (14 episodes maximum). The study coordinator also supplied each subject with a bottle of supplemental antacid.

Study personnel instructed subjects on dosing and filling out the diaries and medication cards. Subjects were instructed to treat only heartburn episodes of moderate or greater severity with study medication. Mild episodes were to be treated with supplemental antacid supplied by the sponsor. Study definitions of mild, moderate, moderately severe, and severe heartburn were provided in the diaries to give guidance to subjects in assessing the severity of their heartburn for study purposes. Subjects were instructed to begin taking the study medication as needed starting at 6:00 AM on the calendar day following the screening visit and continuing for seven consecutive days. Additionally, the medication cards had written instructions telling subjects not to take study medication if they had taken antacids, ASA, NSAIDs, or other analgesics within the previous hour.

b. Visit 2
(Randomization/Double-Blind Period)

At Visit 2, the Investigator reviewed the inclusion/exclusion criteria, and the response to the S-B antacid. For a subject to qualify for randomization, three or more episodes of at least moderate severity must have been treated, and at least 50% of such treated episodes must have been responsive to either single-blind antacid or rescue medication administration at one or more assessment points. Subjects also had to demonstrate the ability to follow the protocol and correctly fill out the diary. Women of child-bearing potential had to have a second negative urine pregnancy test before randomization. The study coordinator repeated the instructions on taking medications, filling out the diary and returning for Visit 3. Subjects were instructed to return with their completed diaries and all other study supplies at Visit 3.

For subjects who did not qualify for randomization, the same procedures were followed as described below under Termination Visit with respect to adverse experiences and discharge from the study.

c. Visit 3
Termination

Subjects returned their completed diaries and other clinical supplies. Study personnel interviewed subjects and reviewed the diaries to elicit possible adverse experiences and information on any changes in concomitant medications. If AEs were reported, they were evaluated by the Investigator for severity, and relationship to the test drug. The date and time of onset, duration, frequency, actions taken and outcome were recorded on the case report form. Subjects were then discharged from the trial.

6. Efficacy/Safety Measures

- Subjects assessed adequacy of HB relief at 15, 30 and 45 min., and 1, 2 and 3 h after each dose of test medication, based on perceived level of discomfort due to the HB.

- Completeness of HB relief was also assessed at the 3-h timepoint.

- AEs were recorded at the end of the S-B and D-B treatment periods.

7. Statistical Procedures

a. Statistical Power and Sample Size

A sample size of approximately 250 subjects per treatment group was planned to achieve 80% power for a two-sided hypothesis test at the 0.05 level. This was based on a subject's sustained adequate relief scores (see section VII.D.2) averaged over the first five episodes. For single episodes, the standard deviation was assumed to be 2 (based on the standard deviation being approximately bounded by half the range of the scale, which was 4) and the between group difference considered to be 0.4. For a single episode, this required about 400 subjects per group. Assuming that the intraclass correlation coefficient was 0.5, the sample size based on the average over five episodes was reduced by 40% to approximately 250 subjects per group.

b. Statistical Methods

- A subject's response profile comprised two components:

  1) whether sustained adequate relief was attained, and
  2) the rapidity with which it was attained.

- For any individual episode of HB, the Sustained Adequate Relief Score (SARS),[4] a categorical score of 0 to 4, was assigned based on the time taken to achieve sustained adequate relief for that particular episode.

[4] Attainment of sustained adequate relief of HB was assigned a value on this 5-point categorical scale as follows:

Value	Time to Relief/Response Time	Duration of Relief
4:	Within 30 mins/Yes response at 15 or 30 mins	Remaining double-blind 3-Hour Treatment Duration
3:	By 1 hour/Yesa response at 45 or 60 mins	Remaining double-blind 3-Hour Treatment Duration
2:	By 2 hours/Yes response at 120 mins	Remaining double-blind 3-Hour Treatment Duration
1:	Within 3 hours/Yes response at 180 mins	No component of sustained relief
0:	No relief within 3 hours/antacid usage anytime	No relief

Examples of SARS Calculations

Subject	Episode #				Average Score
	1	2	3	4	
x	4	4	4	4	4.0
y	2	2	2	2	2.0
z	0	0	0	3	0.75

- A SARS of 0 denoted sustained adequate relief was not attained and/or rescue medication was used.

- A SARS of 4 denoted sustained adequate relief achieved within 30 minutes of treatment.

- Interim scores represented increasing amounts of time taken to reach sustained adequate relief.

- The scores were averaged across episodes within a subject to provide a more precise estimate of these two components of efficacy.

- The primary statistical analysis for efficacy was based on the average across the first four episodes to provide an overall analysis of whether sustained adequate relief of heartburn was attained more frequently and/or sooner in the nizatidine-treated group than in the placebo-treated group.

- Cochran-Mantel-Haenszel tests and generalized estimating equations were used to analyze the data.

- Data from two sets of subjects were analyzed for efficacy. The primary analysis was an intent-to-treat (ITT) analysis using all available data from all randomized subjects who took study medication and provided efficacy data. The secondary analysis, Evaluable Subjects/Evaluable Episodes, included randomized subjects without major protocol violations who took test medication and had at least one evaluable episode.

8. Other Aspects of the Trial

Other aspects of the study, including quality assurance in data collection (monitoring methods, study site personnel training, data verification methods), use of test medication cards and boxes, data handling, etc., were all adequate.

9. Results

a. Enrollment/Disposition of Subjects

- As summarized in Table 3, of a total of 757 enrolled subjects, 209 failed to qualify for randomization[5]. Hence, a total of 541 subjects entered the D-B phase, 274 were randomized to NIZ and 267 were randomized to PL. Four randomized subjects (2 NIZ and 2 PL) failed to provide any safety or efficacy data and were excluded from all analyses. The remaining 537 randomized subjects (272 NIZ and 265 PL) took D-B test medication, provided safety and efficacy data and were included in both the safety and ITT efficacy populations. Of these 537 subjects, 32 were determined to be unevaluable (12 NIZ and 20 PL). The remaining 505 subjects (260 NIZ and 245 PL) qualified for the evaluable population.

5

Number of Subjects Not Qualifying for Randomization by Reason

Reasons for Being Excluded From Randomization	Number
Ineligible	146
Withdrew voluntarily	19
Lost to follow up	13
Protocol violation	13
Uncooperative	12
Administrative/Other	5
Adverse experience	1
Total	209

TABLE 3
Study NZ-95-01

Subject Enrollment/Disposition

Subject Population	Total	Treatment Group	
		PL	NIZ 75 mg
Entered screening	757	---	---
Enrolled in single-blind	757	---	---
Failed to qualify for randomization	209	---	---
Qualified, but withdrew prior to randomization	7	---	---
Entered double-blind	541	267	274
Never Dosed with Test Medication	4	2	2
Included in safety population	537	265	272
Included in intent-to-treat population	537	265	272
Included in evaluable population	505	265	260
Non-evaluable	32 (5.9%)[a]	20 (7.5%)	12 (4.4%)

a) Non-evaluable percent based on total randomized.

- A total of 10 subjects (2 NIZ and 8 PL) discontinued during the D-B period by reasons specified in Table 4.

TABLE 4
Study NZ-95-01

Number of Subjects Discontinuing During
Double-Blind Period by Reason

Reason	Total	Treatment Group	
		PL	NIZ 75 mg
Lost to follow up	2	2	0
Adverse experience	5	4	1
Withdrew voluntarily	2	1	1
Protocol violation	1	1	0
Total	10	8	2

b. Demographic Characteristics and Single-Blind Results

- As shown in Table 5, the Tx groups were comparable for all demographic characteristics.

- The demographic characteristics for those subjects that failed to qualify for randomization into the D-B period of the trial were similar to those of the randomized subjects [sponsor's Table A.2].

- Sponsor's Table A.3 summarized the S-B HB assessment results. Subjects randomized to NIZ or PL during the D-B period had comparable HB assessment results (at the S-B phase). Subjects had, on average, 6 episodes with at least moderate severity. Among these episodes, the average within-subject percentage for which adequate relief was attained was 92% with an average sustained adequate relief score of 2.2. This result is interpreted as indicating that these subjects generally achieved sustained adequate relief between 1 and 2 h of taking antacid.

TABLE 5
Study NZ-95-01

Summary of Subject Demographic Characteristics

Demographic Characteristic		Overall (n=537)	Treatment Group		
			PL (n=265)	NIZ 75 mg (n=272)	p-value
Gender	Men	44%	45%	42%	N.S.
	Women	56%	55%	58%	
Race	Caucasian	83%	84%	82%	
	Black	13%	11%	16%	
	Asian	0%	1%	0%	N.S.
	Hispanic	3%	4%	2%	
	Other	1%	1%	0%	
Age (y)	mean	42	42	42	N.S.
	range				
Weight (lb)	mean	187	186	187	N.S.
	range				
Height (in)	mean	67	67	67	N.S.
	range				
Tobacco use	NO	74%	72%	76%	N.S.
	YES	26%	28%	24%	
Alcohol use	NO	91%	91%	92%	N.S.
	YES	9%	9%	8%	
Caffeine use	NO	23%	19%	26%	N.S.
	YES	77%	81%	74%	

c. Double-Blind Efficacy Results

- There were no significant interactions between treatment and episode number. This indicates that efficacy was generally consistent across episodes.

1) Number of Episodes and Completeness of Data

- Summarized in sponsor's Table B.1 was the frequency of the number of HB episodes treated by subjects, along with the average initial severity of the treated episodes.

- In the ITT population, the number of episodes treated with study medication ranged from [redacted] for both the NIZ and PL-treated subjects with a mean of 10.3 episodes in the NIZ group and 10.0 in the PL group.

- 93% of the subjects had at least 4 episodes (94% of NIZ-treated subjects and 91% of PL-treated subjects).

- The initial severity of the treated episodes was 2.5 (on a 0-4 scale) in both the NIZ and PL groups.

- Sponsor's Table B.2 summarized the number and percentage of episodes for which there were evaluations at each post-dose timepoint.

- Among ITT subjects, 94% percent of NIZ-treated subjects and 96% of the PL-treated subjects recorded HB evaluations through the entire 3-h assessment period. This minimized the need to impute missing values.

TABLE 6
Study NZ-95-01

Sustained Adequate Relief Scores (SARS) Average

Intent-to-Treat Subjects

Episode Interval		PL [n=255]	NIZ 75 mg [n=272]	Therapeutic Gain (NIZ-PL)	Treatment p-value[a]	Treatment-Site Interaction p-value
First 4 Episodes	n	265	272			
	Mean	2.15	2.45	0.30		
	Std	1.16	1.09		0.002	0.037
	Median	2.00	2.50	0.50		
	Range	[redacted]				
All Episodes	n	265	272			
	Mean	2.13	2.46	0.33		
	Std	1.11	1.02		<0.001	N.S.
	Median	2.22	2.52	0.30		
	Range	[redacted]				

a) Cochran-Mantel-Haenszel row mean score test controlling for site

2) Intent-To-Treat Analysis: Primary Efficacy Endpoint

- The results for the SARS averaged over a subject's first episodes[6] are given in Table 6 which corresponds to sponsor's Table B.3. NIZ 75 mg demonstrated a strong statistically significant advantage over PL, with a mean SARS therapeutic gain of 0.30 averaged over the first 4 episodes.

- Subjects treated with NIZ achieved sustained adequate relief sooner and/or more consistently than those treated with PL.

- As illustrated in Table 7 (sponsor's Table B.4) this same strong significant effect of NIZ was observed when the SARS from *all* episodes were analyzed using a generalized estimating equation (GEE) linear model.

TABLE 7
Study NZ-95-01

Summary of GEE[a] Analyses

Intent-to-Treat Subjects

Efficacy Endpoint	Treatment Effect	Treatment p-value	Treatment-Site Interaction p-value	Treatment-Episode Interaction p-value
SARS (All Episodes)[b]	0.34 (0.09)[c]	<0.001	<0.001	N.S.
SARS, Regardless of Time (All Episodes)[d]	0.73 (0.13)	<0.001	0.016	N.S.
Rescue Medication Use (All Episodes)[d]	-0.70 (0.15)	<0.001	N.S.	N.S.
Complete Relief Reported at 3 h (All Episodes)[d]	0.73 (0.13)	<0.001	<0.001	N.S.
Adequate Relief by -- min. (All episodes)[d]				
15	-0.21 (0.20)	N.S.	0.019	N.S.
30	0.02 (0.15)	N.S.	0.030	N.S.
45	0.20 (0.14)	N.S.	0.026	N.S.
60	0.40 (0.14)	0.004	0.004	N.S.
120	1.10 (0.13)	<0.001	<0.001	N.S.
180	1.12 (0.13)	<0.001	<0.001	N.S.

a) GEE = Generalized Estimating Equation
b) Linear model - treatment effect is interpreted as the mean difference between NIZ and PL adjusting for the effects in the model
c) S.E.
d) Logistic model - treatment effect is interpreted as the log (odds ratio) for NIZ versus PL

NOTE: Models contained effects for treatment, baseline severity of episode, episode number, treatment episode number, site and treatment site

[6] The site-by-treatment interaction was significant (p=0.037) in the analysis of the average over the first four episodes, mostly because in five of the 21 analyzed sites there was a numerical advantage for PL. The results were fairly consistent among the 16 sites where NIZ had a numerical advantage, without any individual site clearly accounting by itself for NIZ overall superiority to PL.

3) Intent-To-Treat Analysis: Secondary Efficacy Endpoints

a) Sustained Adequate Relief Scores Averaged Over All Episodes Within Each Subject (Table 6)

As shown in the lower section of this Table, across all episodes, NIZ provided significantly sooner and/or more consistent relief than PL, with a therapeutic gain of 0.33 mean score.

[The GEE analysis of this endpoint is discussed below and confirms NIZ's benefit over PL in providing consistent, more rapid HB relief].

b) Proportion of Episodes Within Each Subject for Which Sustained Adequate Relief Was Attained Regardless of Time (Table 8)

For both the first 4 and all episodes, subjects using NIZ attained sustained adequate relief for about 76% of their episodes, significantly more often than subjects using placebo, who attained it for about 66% of their episodes [therapeutic gain=10%, p<0.001].

[The results for all episodes were confirmed (p<0.001) by a GEE logistic model assessing whether or not an episode was adequately relieved (Table 7)].

TABLE 8
Study NZ-95-01

Proportion of Each Subject's Episodes for Which SAR Was Attained

Intent-to-Treat Subjects

Episode Interval		PL [n=255]	NIZ 75 mg [n=272]	Therapeutic Gain (NIZ-PL)	Treatment p-value[a]	Treatment-Site Interaction p-value
First 4 Episodes	n	265	272			
	Mean	0.66	0.76	0.10		
	Std	0.32	0.28		<0.001	N.S.
	Median	0.75	0.75	0.00		
	Range					
All Episodes	n	265	272			
	Mean	0.66	0.76	0.10		
	Std	0.30	0.26		<0.001	N.S.
	Median	0.70	0.82	0.12		
	Range					

a) Cochran-Mantel-Haenszel row mean score test controlling for site

c) Sustained Adequate Relief Scores Averaged Over a Subject's First 4 Episodes Each of Which Was Separated by at Least 12 h (Table 9)

- As shown in this Table, NIZ provided significantly more HB relief with a mean score of 2.44 compared to placebo with a mean score of 2.15 [therapeutic gain=0.29 mean score], for episodes separated by at least 12 h. This indicates that NIZ efficacy was provided by single doses and was not due to a cumulative treatment effect.

- The site-by-treatment interaction was significant (p=0.035), mostly because there was a numerical advantage for PL in six of the 21 analyzed sites. The results were fairly consistent among the 15 sites where NIZ had a numerical advantage, without any individual site clearly accounting by itself for NIZ's overall superiority to PL.

TABLE 9
Study NZ-95-01

SARS Averaged Over First Four Episodes Separated by at Least 12 h

Intent-to-Treat Subjects

Episode Interval		PL [n=265]	NIZ 75 mg [n=272]	Therapeutic Gain (NIZ-PL)	Treatment p-value[a]	Treatment-Site Interaction p-value
First 4 Episodes	n	265	272			
	Mean	2.15	2.44	0.29		
	Std	1.19	1.10		0.003	0.035
	Median	2.25	2.50	0.25		
	Range					

a) Cochran-Mantel-Haenszel row mean score test controlling for site.

NOTE: The protocol indicated that in order to minimize any possible carryover effect, the average SARS for each subject was to be calculated over the first K episodes each of which followed the previous episode by at least 12 h, where k is the maximum number of episodes up to five for which at least 90% of the subjects had evaluations. This number was determined to be four (94% in the NIZ group, 89% in the PL group).

d) Proportion of Episodes Within Each Subject With Adequate Relief at Each Timepoint (Table 10)

- Results of the analysis of the proportion of episodes within each subject for which adequate relief was attained at each timepoint (regardless of whether it was sustained) are presented in this Table (I., upper panel, for the first 4 episodes and II., lower panel for all episodes.

- Figure 1 (upper graph) illustrates the results based on the first 4 episodes, the results based on all episodes are illustrated in the lower graph of this Figure.

- For both the first four and all episodes, NIZ-treated subjects had significantly more episodes adequately relieved than did placebo-treated subjects at 60 minutes. The therapeutic gains (0.09 and 0.10 for the first 4 episodes and 0.10 and 0.10 for all episodes) were strongly significantly more at 120 and 180 min. (Table 10).

  [The results for all episodes were confirmed using a GEE logistic model (Table 7)].

- In the analysis based on all episodes, the site-by-treatment interaction was significant (p=0.048) at the 60 min. timepoint, most because PL was favored over NIZ in five of the 21 analyzed sites.

- The results were fairly consistent among the 16 sites where NIZ had a numerical advantage, without any individual site clearly accounting by itself for NIZ's overall superiority to PL.

TABLE 10
Study NZ-95-01

Mean Proportion of Each Subject's Episodes for Which Adequate Relief was Attained by Time Point

Intent-to-Treat Subjects

Minutes After Dosing with Study Medication	PL [n=265]	NIZ 75 mg [n=272]	Therapeutic Gain	Treatment p-value[a]	Treatment-Site Interaction p-value
I. Based on the First 4 Episodes					
15	0.17	0.16	-0.01	N.S.	N.S.
30	0.34	0.34	None	N.S.	N.S.
45	0.51	0.56	0.05	N.S.	N.S.
60	0.64	0.71	0.07	0.033	N.S.
120	0.69	0.78	0.09	<0.001	N.S.
180	0.67	0.77	0.10	<0.001	N.S.
II. Based on All Episodes					
15	0.18	0.16	-0.02	N.S.	N.S.
30	0.33	0.34	0.01	N.S.	N.S.
45	0.51	0.55	0.04	N.S.	N.S.
60	0.64	0.71	0.07	0.007	0.048
120	0.69	0.79	0.10	<0.001	N.S.
180	0.67	0.77	0.10	<0.001	N.S.

a) Cochran-Mantel-Haenszel row mean score test controlling for site

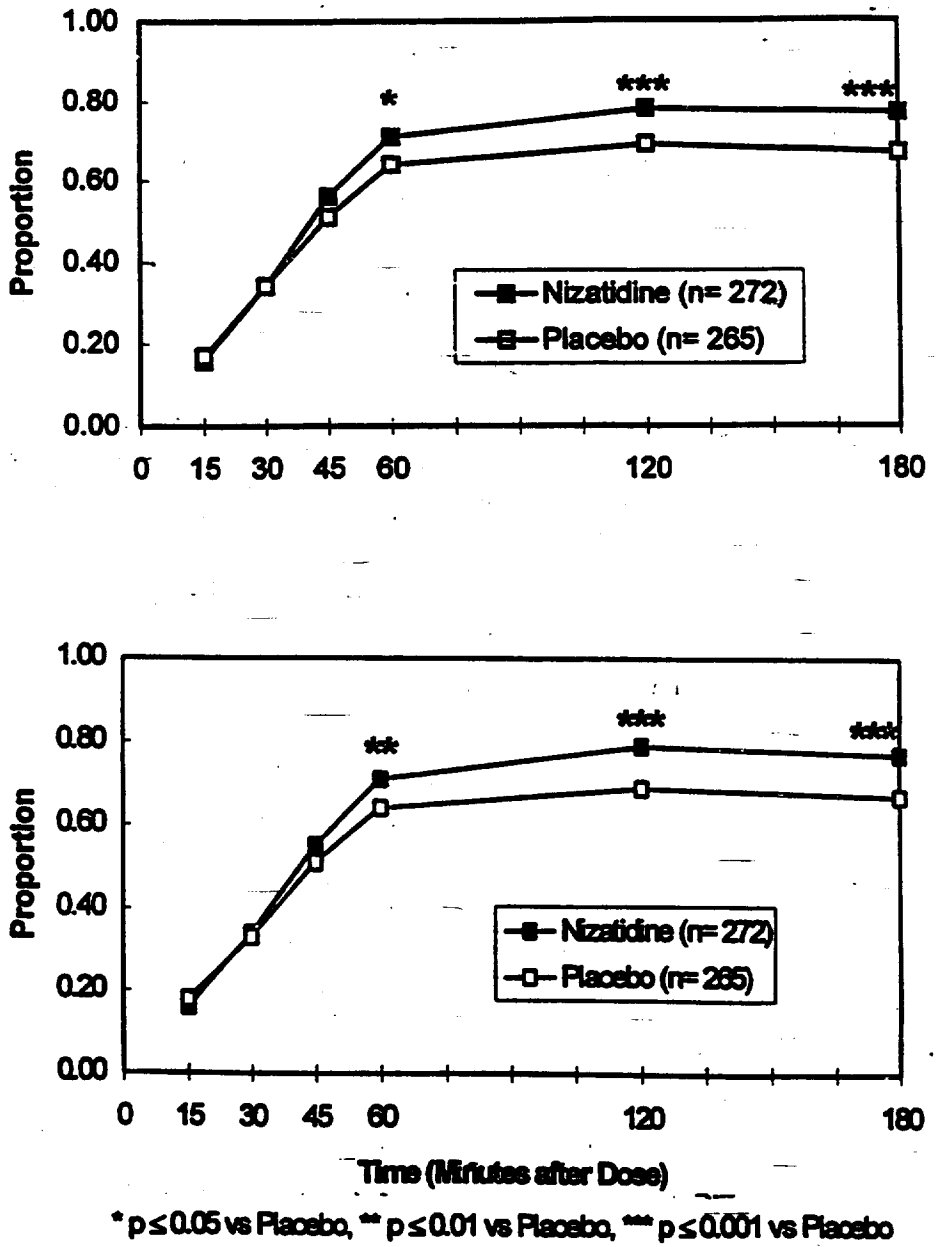

Fig. 1. - Study NZ-09-01: Proportion of Episodes with Adequate Relief at Each Timepoint Based on the First 4 Episodes (upper graph) or on All Episodes (lower graph).

e) Proportion of Episodes Within Each Subject for Which Rescue Medication Was Taken (Table 11)

NIZ-treated subjects took rescue medication for a significantly lower proportion of both their first four episodes and all episodes than did PL-treated subjects (mean therapeutic gain of 8% for the first 4 episodes; 10% for all episodes).

[The results for all episodes were confirmed using a GEE logistic model (Table 7)

TABLE 11
Study NZ-95-01

Proportion of Each Subject's Episodes for Which Rescue Medication Was Taken

Intent-to-Treat Subjects

Episode Interval		PL [n=265]	NIZ 75 mg [n=272]	Therapeutic Gain (NIZ-PL)	Treatment p-value[a]	Treatment-Site Interaction p-value
First 4 Episodes	n	265	272			
	Mean	0.27	0.19	-0.08		
	Std	0.31	0.27		0.002	N.S.
	Median	0.25	0.00	-0.25		
	Range	[redacted]				
All Episodes	n	265	272			
	Mean	0.28	0.18	-0.10		
	Std	0.29	0.24		<0.001	N.S.
	Median	0.23	0.10	-0.13		
	Range	[redacted]				

a) Cochran-Mantel-Haenszel row mean score test controlling for site

f) Proportion of Episodes Within Each Subject for Which Complete Relief Was Reported at the 3-h Timepoint (Table 12)

NIZ-treated subjects reported complete relief in a significantly higher proportion of both their first four episodes and all episodes than did placebo-treated subjects (mean therapeutic gain of 9% for first 4 as well as for all episodes). [Thus, NIZ provided not only significantly more adequate relief, but also significantly more complete relief than PL.]

[These results for all episodes were confirmed with the GEE analysis and can be found in Table 7.]

TABLE 12
Study NZ-95-01

Proportion of Each Subject's Episodes for Which Complete Relief was Reported at the 3-h Time Point

Intent-to-Treat Subjects

Episode Interval		PL [n=265]	NIZ 75 mg [n=272]	Therapeutic Gain (NIZ-PL)	Treatment p-value[a]	Treatment-Site Interaction p-value
First 4 Episodes	n	265	272			
	Mean	0.65	0.74	0.09		
	Std	0.32	0.30		<0.001	N.S.
	Median	0.75	0.75	None		
	Range	[redacted]				
All Episodes	n	265	272			
	Mean	0.65	0.74	0.09		
	Std	0.30	0.28		<0.001	N.S.
	Median	0.70	0.80	0.10		
	Range	[redacted]				

a) Cochran-Mantel-Haenszel row mean score test controlling for site

g) Sustained Adequate Relief Score for the First Episode (Table 13)

Adequate HB relief in the first episode was attained significantly sooner in the NIZ-treated subjects with a mean SARS of 2.50 compared to PL with a mean of 2.08 (therapeutic gain=score of 0.42).

TABLE 13
Study NZ-95-01

SARS for the First Episode [%]

Intent-to-Treat Subjects

Sustained Relief Attained:	PL [n-265]	NIZ 75 mg [n=272]	Therapeutic Gain (NIZ-PL)	Treatment p-value[a]	Treatment-Site Interaction p-value
At 15 or 30 Min. (4)	77 (29%)	88 (32%)	3%	0.003	N.S.
At 45 or 60 Min. (3)	69 (26%)	90 (33%)	7%		
At 120 Min. (2)	15 (6%)	28 (10%)	4%		
At 180 Min. (1)	7 (3%)	3 (1%)	- 2%		
Not Within 3h or Rescue Medication Taken (0)	97 (31%)	63 (23%)	-14%		
Mean of Sustained Adequate Relief Scores	2.1	2.5	0.4		

a) Cochran-Mantel-Haenszel row mean score test controlling for site

h) Percentage of Subjects Achieving Sustained Adequate Relief at All Recorded Episodes (Table 14)

A significantly higher percentage (therapeutic gain=10%) of NIZ-treated subjects had sustained adequate relief at all of their episodes than did PL-treated subjects.

TABLE 14
Study NZ-95-01

Number (%) of Subjects Achieving SAR for All Recorded Episodes (%)

Intent-to-Treat Subjects

	PL [n=265]	NIZ 75 mg [n=272]	Therapeutic Gain (NIZ-PL)	Treatment p-value[a]	Treatment-Site Interaction p-value
Subjects Achieving SAR for All Episodes					
NO	198 (75%)	178 (65%)	-10%	0.019	N.S.
YES	67 (25%)	94 (35%)	10%		

a) Cochran-Mantel-Haenszel general association test controlling for site

i) Percentage of Subjects Achieving Complete Relief at All Recorded Episodes (Table 15)

A significantly higher percentage of NIZ-treated subjects had complete relief at all of their episodes than did PL-treated subjects (35% versus 24%). This represents a therapeutic gain of 11%.

TABLE 15
Study NZ-95-01

Number (%) of Subjects Achieving Complete Relief for All Recorded Episodes (%)

Intent-to-Treat Subjects

	PL [n=265]	NIZ 75 mg [n=272]	Therapeutic Gain (NIZ-PL)	Treatment p-value[a]	Treatment-Site Interaction p-value
Subjects Achieving Complete Relief for All Episodes					
NO	201 (76%)	176 (65%)	-11%	0.005	N.S.
YES	64 (24%)	94 (35%)	11%		

a) Cochran-Mantel-Haenszel general association test controlling for site

4) Within-Investigator Results[7]

- The variables analyzed were:

  1) SARS Averaged over a subject's first four episodes,

  2) Proportion of episodes within each subject for which sustained adequate relief was attained based on the first four episodes.

  3) Proportion of subjects achieving sustained adequate relief for all episodes, and

  4) Proportion of episodes within each subject for which complete relief was reported based on the first four episodes.

- Results showed NIZ's superiority to PL was generally consistent across the sites, without any individual site clearly accounting by itself for this superiority.

5) Intent-to-Treat Subgroup Analyses

- Efficacy analyses done using data from subgroups based on HB frequency, HB episode severity, and success of antacid use (based on the single-blind phase of the study) are summarized in Table 16.

- The subgroup analyses according to HB frequency and antacid use were based on the subject's first 4 episodes; the subgroup analysis according to the severity of HB episodes was based on all episodes.

- This reviewer agrees with the sponsor that NIZ was superior to PL within all the subgroups by significant or borderline significant amounts despite the reduced sample size within the subgroups. No clear differences across subgroups were apparent.

[7] For selected variables, summaries of the results within investigator were found in sponsor's Tables B.13 through B.16, while their Figures B.1 through B.4 contained the site-specific treatment differences and 95% confidence intervals for these differences. The full set of within-investigator results were in sponsor's Appendix VII.

TABLE 16
Study NZ-95-01

Subgroup Analyses of SARS

Subgroup	PL Mean (n)	NIZ 75 mg Mean (n)	p-value
HB Frequency			
≤ 10 Episodes	2.19 (164)	2.47 (173)	0.017
> 10 Episodes	2.09 (101)	2.42 (99)	0.084
HB Severity[a]			
Moderate	2.42 (230)	2.78 (239)	<0.001
Moderately Severe/Severe	1.69 (217)	2.01 (219)	0.004
Antacid Use			
<75% episodes adequately relieved using antacid	1.83 (31)	1.94 (31)	0.060
≥75% episodes adequately relieved using antacid	2.20 (234)	2.51 (241)	0.002

a) Since this subgrouping is by episode, some subjects are in both the moderate and the moderately severe/severe subgroups.

6) Evaluable Analyses[8]

These results were similar to those discussed for the ITT population. The pattern of significant results was nearly identical to those in the intent-to-treat analysis.

d. Safety Results

- Study NZ-95-01 showed that NIZ was safe and well tolerated.
- No serious, unexpected AEs or deaths due to test medication occurred in this trial.
- There was no significant difference between the treatment groups in the number of AEs.
- The most common AEs in the NIZ group were headache, diarrhea and dyspepsia.
- This AE profile is similar to that reported for NIZ in the submission for prevention of heartburn (NDA 20-555, Vol 1.70, p 08-20306).

[8] The results for the evaluable population were presented in sponsor's Tables B.20 through B.29.

10. Sponsor's Conclusions

"The clear benefit of nizatidine in the treatment of episodic heartburn was demonstrated in this study. Its efficacy has been shown and was robust in its consistency across all parameters analyzed. Nizatidine 75mg was safe and well-tolerated when taken up to twice a day for the treatment of episodic heartburn."

11. Reviewer's Additional Comments/Conclusions

Study NZ-95-01 is one of two pivotal symptom treatment trials (the other was NZ-95-04) submitted by the sponsor of this NDA to demonstrate the efficacy and safety of NIZ 75 mg in relieving episodic heartburn, when taken as needed up to twice daily, compared to placebo.

The trial was well-designed (double-blind, randomized, parallel, single dose), well controlled (PL) and apparently well executed.

The study population was adequate. It consisted of generally healthy subjects, 16y of age or older who had a Hx of a minimum 3-months of at least moderate HB, who ordinarily used OTC antacid and/or OTC histamine H_2-receptor antagonist for the treatment of their HB. In this study, efficacy parameters assessed rapidity, consistency and extent of HB relief perceived by the subjects. The most important (primary) efficacy endpoint was the mean sustained relief score (SARS) averaged over the first 4 episodes for each subject. The MO agrees with the sponsor that this approach gave a more precise estimate of an individual subject's response since both the elements of achievement of sustained relief and the rapidity with which it was attained were incorporated.

The MO's detailed evaluation of the patients' baseline characteristics demonstrated that the two experimental groups were essentially comparable (to each other) in demographic, HB Hx, Medical Hx and additional background characteristics. Since there were no clinically significant pre-drug differences between the Tx groups, it is appropriate to assess comparative efficacy and safety analyses. Furthermore, the randomized study population was representative of the broad screening population.

In this study, single doses of NIZ 75 mg were clearly superior to PL in providing faster and/or more reliable HB relief (therapeutic gain 0.30, p=0.002 when the mean SARS averaged over the first 4 episodes were compared. This same significant advantage for NIZ-treated subjects persisted when the SARS was calculated over all episodes within subjects. Moreover, the advantage of NIZ was statistically demonstrable even for the first episodes in spite of the fact that this assessment had reduced statistical power (smaller). Furthermore, NIZ's significant advantage over PL was also shown when the SARS was averaged over the subjects first four episodes that were separated by at least 12h. Since this 12h-interval is well over 5 times the elimination half-life of the drug (1 to 2h), these findings mean that NIZ's effectiveness is provided with single doses rather than a cumulative dose effect over time.

NIZ's superiority to PL was also shown when efficacy was assessed as proportion of episodes for which sustained adequate relief was attained, regardless of time, both among the first four and over all episodes. Subjects taking NIZ attained relief for 76% of their episodes, significantly more often than subjects taking PL, who attained relief for 66% of their episodes (therapeutic gain = 10%, p<0.001). It is however important to note that NIZ's effectiveness relative to PL became apparent at 60 min. after dosing and was significant through the end of the assessment period. NIZ was also significantly better than PL at providing relief at all episodes. Over one-third (35%) of the NIZ subjects experienced sustained adequate relief at *all* episodes, while this was true for one fourth (25%) of PL-treated subjects (therapeutic gain = 10%, p=0.019). NIZ also provided complete relief significantly more often than did PL, both in terms of the mean proportion of episodes completely relieved, 74% for NIZ-treated subjects compared to 65% for PL-treated subjects (therapeutic gain = 9%, p<0.001), and in the proportion of subjects with complete relief at *all* their episodes (therapeutic gain = 11%, p=0.005).

In summary, the MO agrees with the sponsor's conclusions about study NZ-95-01. The trial showed that NIZ 75 mg provided sustained adequate relief sooner and/or more consistently than the negative comparator. At the 75 mg dose, the drug also provided complete relief more consistently than PL. In addition, this study showed that up to twice a day, doses of NIZ, 75 mg, were well tolerated.

VIII. STUDY NZ-95-04

"RELIEF OF EPISODIC HEARTBURN: SAFETY AND EFFICACY OF NIZATIDINE 75mg - A PLACEBO-CONTROLLED STUDY"

- The study dates were March 1996 - September 1996 and the report date November 1996. The trial was carried out in accordance with GCP by a [redacted]

- As summarized in Table 1, this second pivotal study used an identical protocol to that in study NZ-95-01. Therefore, the objectives, study design and study population were as in study NZ-95-01. The clinical supplies used in study NZ-95-04 were as summarized below.

Study NZ-95-04: Test Medication

Period	Study Drug	Per Tablet	Per Dose	Lot Number
Single-blind	Single-blind Antacid[a]	480 mg (13.5 mEq)	480 mg (13.5 mEq)	WH-678-001A WH-678-001B
	Rescue Medication[b]	500 mg (10.3 mEq)	500 mg (10.3 mEq)	WH-464-009A WH-464-009B
Double-blind	NIZ	75 mg	75 mg	WH-463-13W
	PL	Inert Ingredients	Inert Ingredients	WH-463-15D
	Rescue Medication[b]	500 mg (10.3 mEq)	500 mg (10.3 mEq)	WH-464-009A WH-464-009B
Both periods: interim episodes of heartburn	Supplemental Antacid[c]	500 mg (10.3 mEq)	500 mg (10.3 mEq)	WH-0692-001A WH-0692-001B

[redacted]
b) Tums® repackaged on medication cards
c) Tums® provided in commercial packaging

- Equally similar to those in study NZ-95-01, were the methods of randomization, blinding, labeling, storage and accountability and the handling of concomitant medications.

- The Clinical Procedures/Observations were those as described under 5. for study NZ-95-01. In essence, study NZ-95-04 was an at home, multi-center, randomized, D-B, PL-controlled, balanced-parallel-group design lasting three weeks. Subjects treated up to two episodes of moderate to severe HB daily for one week in the S-B antacid qualifying period and for two weeks in the D-B treatment period. Each treated episode was evaluated over 3h at 15, 30, 45 minutes, 1, 2 and 3 h after dosing. Subjects who had insufficient relief were permitted to take rescue medication after the 2-h post-dose assessment. A 4-h interval from the start of study medication and resolution of the previous episode was required before treating a second episode on any one day of the study. A sample size of ca. 500 subjects (250 per treatment group) was needed to achieve 80% power for rejecting a two-sided null hypothesis test at the 0.05 level. In the event that the study population reached 460 subjects completing the D-B treatment period before August 30, 1996, further enrollment in the trial could have been terminated before the planned enrollment number was reached.

- The Efficacy/Safety measures were adequate as in study NZ-95-01. Subjects assessed adequacy of HB relief at 15, 30 and 45 min. and 1, 2 and 3h after each dose of test medication, based on perceived level of discomfort due to the HB. Completeness of HB relief was also assessed at the 3-h timepoint. AEs were recorded and the S-B and D-B treatment periods.

- The primary and secondary endpoints of efficacy and the Statistical Procedures and other aspects of the trial were the same as in study NZ-95-01.

9. Results

a. Enrollment/Disposition of Patients

- As summarized in Table 17, of a total of 666 enrolled subjects, 191 failed to qualify for randomization[9] and another 10 withdrew prior to randomization. Hence, a total of 465 subjects entered the D-B phase, 230 were randomized to NIZ and 235 were randomized to PL. Eight randomized subjects (4 NIZ and 4 PL) did not take any study medication or failed to provide any safety or efficacy data and were excluded from all analyses. The remaining 457 randomized subjects (226 NIZ and 231 PL) took D-B test medication, provided safety and efficacy data and were included in both the safety and ITT efficacy populations. Of these 457 subjects, 49 subjects were determined to be unevaluable (22 NIZ and 27 PL). The remaining 408 subjects (204 NIZ and 204 PL) qualified for the evaluable population.

[9]

Number of Subjects Not Qualifying for Randomization by Reason

Reasons for Being Excluded From Randomizations	Number
Ineligible	131
Withdrew voluntarily	19
Lost to follow-up	14
Protocol violation	13
Uncooperative	10
Administrative/Other	2
Adverse experience	2
Total	191

TABLE 17
Study NZ-95-04

Subject Enrollment/Disposition

Subject Population	Total	Treatment Group	
		PL	NIZ 75 mg
Entered screening	666	---	---
Enrolled in single-blind	666	---	---
Failed to qualify for randomization	191	---	---
Qualified, but withdrew prior to randomization	10	---	---
Entered double-blind	465	235	230
Never dosed with test medication	8	4	4
Included in safety population	457	231	226
Included in Intent-to-Treat population	457	231	226
Included in Evaluable population	408	204	204
Non-evaluable	49 (10.5%)[a]	22 (9.6%)	27 (11.5%)

a) Non-evaluable percent based on total randomized

- A total of 12 subjects (6 NIZ, 6 PL) discontinued during the D-B period for reasons specified in Table 18.

TABLE 18
Study NZ-95-04

Number of Subjects Discontinuing During Double-Blind Period by Reason

Reasons Subjects Discontinued From Double-Blind	Total	Treatment Group	
		PL	NIZ 75 mg
Lost to follow-up	3	2	1
Adverse experience**	2	0	2
Withdrew voluntarily	2	1	1
Protocol violation	5	3	2
Total	12	6	6

b. Demographic Characteristics and Single-Blind Results

- As seen in Table 19, the Tx groups were comparable for all demographic characteristics.

- The demographic characteristics for those subjects that failed to qualify for randomization into the D-B period of the trial were similar to those of the randomized subjects [sponsor's Table A.2].

TABLE 19
Study NZ-95-04

Summary of Subject Demographic Characteristics

Demographic Characteristic			Treatment Group		
		Overall [n=457]	PL [n=231]	NIZ 75 mg [n=226]	p-value
Gender	Men	48%	49%	47%	N.S.
	Women	52%	51%	53%	
Race	Caucasian	80%	79%	81%	N.S.
	Black	8%	8%	8%	
	Asian	2%	3%	1%	
	Hispanic	9%	10%	9%	
	Other	1%	1%	1%	
Age (y)	mean	44	45	43	N.S.
	range				
Weight (lb)	mean	187	187	186	N.S.
	range				
Height (in)	mean	67	67	67	N.S.
	range				
Tobacco use	NO	77%	79%	75%	N.S.
	YES	23%	21%	25%	
Alcohol use	NO	91%	92%	91%	N.S.
	YES	9%	8%	9%	
Caffeine use	NO	25%	26%	23%	N.S.
	YES	75%	74%	77%	

- Sponsor's Table A.3 summarized the S-B HB assessment results. Subjects randomized to NIZ or PL during the double-blind period had comparable HB assessment results (at the S-B phase). Subjects had, on average, 6 episodes with at least moderate severity. Among these episodes, the average within-subject percentage for which adequate relief was attained was 89%, with an average sustained adequate relief score of 2.2. This result means that these subjects generally achieved sustained adequate relief between 1 and 2 h of taking antacid.

c. Double-Blind Efficacy Results

- There were no significant interactions of treatment and site in any of the analyses except where noted. Efficacy did not seem consistent across episodes (see below).

1) Number of Episodes and Completeness of Data

- Summarized in sponsor's Table B.1 was the frequency of the number of HB episodes treated by subjects, along with the average initial severity of the treated episodes.

- In the ITT population, the number of episodes treated with study medication ranged from [redacted] for both the NIZ and PL-treated subjects with a mean of 10.2 episodes in the NIZ group and 10.4 in the PL group.

- 92% of the subjects had at least 4 episodes (91% of NIZ-treated subjects and 92% of PL-treated subjects).

- The initial severity of the treated episodes was 2.5 (on a 0-4 scale) in both the NIZ and PL groups.

- Sponsor's Table B.2 summarized the number and percentage of episodes for which there were evaluations at each post-dose timepoint.

- Among ITT subjects, 93% of NIZ-treated subjects and 94% of the PL-treated subjects recorded HB evaluations through the entire 3-h assessment period. This minimized the need to impute missing values.

2) Intent-to-Treat Analysis: Primary Efficacy Endpoint

- The results for the SARS averaged over a subject's first 4 episodes are given in Table 20 [which corresponds to sponsor's Table B.3]. NIZ 75 mg demonstrated a statistically significant advantage over PL with a mean SARS therapeutic gain of 0.28 averaged over the first 4 episodes.

- Subjects treated with NIZ achieved sustained adequate relief sooner and/or more consistently than those treated with PL.

TABLE 20
Study NZ-95-04

Sustained Adequate Relief Scores (SARS) Average

Intent-to-Treat Subjects

Episode Interval		PL [n=231]	NIZ 75 mg [n=226]	Therapeutic Gain (NIZ-PL)	Treatment p-value[a]	Treatment-Site Interaction p-value
First 4 Episodes	n	231	226			
	Mean	2.11	2.39	0.28		
	Std	1.24	1.25		0.016	N.S.
	Median	2.25	2.75	0.50		
	Range					
All Episodes	n	231	226			
	Mean	2.11	2.35	0.24		
	Std	1.15	1.21		0.028	N.S.
	Median	2.18	2.67	0.49		
	Range					

a) Cochran-Mantel-Haenszel row mean score test controlling for site

- Tabulated in Table 21 [which corresponds to sponsor's Table B.4] are results of analyses carried out to determine if the superior efficacy based on the first four episodes extended to all episodes for NIZ. The SARS from all episodes were analyzed using a generalized estimating equation (GEE) linear model.

- The GEE analysis based on the model including treatment-by-site and treatment-by-episode number interactions showed NIZ was only numerically (but not statistically) superior over PL with a model-fitted treatment difference of 0.16 (p=N.S.).

- The sponsor argues that although inclusion of the interactions is often appropriate, it can result in small cells (sites or episode number categories with a small number of subjects) having an unduly large influence. This seems like a reasonable explanation for these findings.

- The PL group showed a numerical advantage over NIZ in seven sites, all of which were relatively small. This also caused a significant treatment-by-site interaction.

- An additional GEE analysis was performed by the sponsor based on a model without the above interactions to allow for the similar weighting scheme as the CMH analysis, i.e., larger cells have larger weights. This analysis was consistent with the CMH analysis and showed that NIZ was significantly superior to PL with a model-fitted treatment difference of 0.25 (p=0.034).

TABLE 21
Study NZ-95-04

Summary of GEE[a] Analyses

Intent-to-Treat Subjects

Efficacy Endpoint	Treatment Effect	Treatment p-value	Treatment-Site Interaction p-value	Treatment-Episode Interaction p-value
SARS (All Episodes)[b]	0.16 (0.12)[c]	N.S.	0.045	0.045
SAR, Regardless of Time (All Episodes)[d]	0.38 (0.15)	0.011		
Rescue Medication Use (All Episodes)[d]	-0.46 (0.15)	0.003		
Complete Relief Reported at 3 h (All Episodes)[d]	0.47 (0.15)	0.002		
Adequate Relief by -- Min. (All Episodes)[d]				
15	0.09 (0.19)	N.S.	Not Calculated by the Sponsor	
30	-0.01 (0.15)	N.S.		
45	0.07 (0.14)	N.S.		
60	0.23 (0.14)	N.S.		
120	0.34 (0.15)	0.022		
180	0.39 (0.15)	0.008		

a) GEE = Generalized Estimations Equation
b) Linear model - treatment effect is interpreted as the mean difference between NIZ and PL adjusting for the effects in the model
c) S.E.
NOTE: This model contained effects for treatment, baseline severity of episode, episode number, treatment episode number, site and treatment site
d) Logistic model - treatment effect is interpreted as the log (odds ratio) for NIZ versus PL
NOTE: This model contained effects for treatment, baseline severity of episode, episode number, and site

3) Intent-to-Treat Analysis: Secondary Efficacy Endpoints

a) Sustained Adequate Relief Scores Averaged Over All Episodes Within Each Subject (Table 20)

NIZ provided significantly sooner and/or more consistent relief with a therapeutic gain of 0.4 mean score.

[The GEE analysis of this endpoint is discussed below; this analysis confirms NIZ's benefit over PL in providing consistent, more rapid HB relief.]

b) Proportion of Episodes Within Each Subject for Which Sustained Adequate Relief Was Attained Regardless of Time (Table 22)

For the first 4 episodes, subjects using NIZ attained sustained adequate relief for 74% of their episodes, significantly more often than subjects using PL, who attained it for 66% of their episodes [therapeutic gain=8%, p=0.014]. For all episodes, subjects using NIZ attained sustained adequate relief for 73% of their episodes, significantly more often than subjects using PL, who attained it for 66% of their episodes [therapeutic gain=7%, p=0.027].

[The results for all episodes were confirmed by a GEE[10] logistic model assessing whether or not an episode was adequately relieved (Table 21)]

TABLE 22
Study NZ-95-04

Proportion of Each Subject's Episodes for Which SAR was Attained

Intent-To-treat Subjects

Episode Interval		PL [n=231]	NIZ 75 mg [n=226]	Therapeutic Gain (NIZ-PL)	Treatment p-value[a]	Treatment-Site Interaction p-value
First 4 Episodes	n	231	226			
	Mean	0.66	0.74	0.08		
	Std	0.33	0.34		0.014	N.S.
	Median	0.75	1.00	0.25		
	Range	[redacted]				
All Episodes	n	231	226			
	Mean	0.66	0.73	0.07		
	Std	0.31	0.33		0.027	N.S.
	Median	0.72	0.84	0.12		
	Range	[redacted]				

a) Cochran-Mantel-Haenszel row mean score test controlling for site

c) Sustained Adequate Relief Scores Averaged Over a Subject's First 4 Episodes Each of Which Was Separated by at Least 12 h (Table 23)

- As shown in this Table, NIZ provided significantly more HB relief with a mean score of 2.39 compared to placebo with a mean score of 2.12 [therapeutic gain=0.27], for episodes separated by at least 12 h. This

[10] The sponsor argues that, as stated in the statistical methods section VII.D.3 (of their Clinical Report), in all GEE logistic analyses the model without interaction terms for treatment-by-site and treatment-by-episode number was used, since including these interactions resulted in non-convergence of the parameter estimation. However, had this model converged, it is possible that NIZ would not have been significantly better than PL, primarily because the model with the interactions gives unduly large weights to the small cells, which tended to favor PL. This appears to be a reasonable explanation.

indicates that NIZ efficacy was provided by single doses and was not due to a cumulative treatment effect.

TABLE 23
Study NZ-95-04

SARS Averaged Over First Four Episodes Separated by at Least 12 h

Intent-to-Treat Subjects

Episode Interval		PL [n=231]	NIZ 75 mg [n=226]	Therapeutic Gain (NIZ-PL)	Treatment p-value[a]	Treatment-Site Interaction p-value
First 4 Episodes	n	231	226			
	Mean	2.12	2.39	0.27		
	Std	1.25	1.26		0.020	N.S.
	Median	2.25	2.75	0.50		
	Range					

a) Cochran-Mantel-Haenszel row mean score test controlling for site

NOTE: The protocol indicated that in order to minimize any possible carryover effect, the average SARS for each subject was to be calculated over the first k episodes each of which was separated by at least 12 h, where k is the maximum number of episodes up to five for which at least 90% of the subjects had evaluations. This number was determined to be 4 (94% in the NIZ group, 89% in the PL group).

d) Proportion of Episodes Within Each Subject With Adequate Relief at Each Timepoint (Table 24)

- Results of the analysis of the proportion of episodes within each subject for which adequate relief was attained at each timepoint (regardless of whether it was sustained) are presented in this Table (I., upper panel, for the first 4 episodes and II., lower panel for all episodes).

- Figure 2 (upper graph) illustrates the results based on the first 4 episodes; the results based on all episodes are illustrated in the lower graph of this Figure.

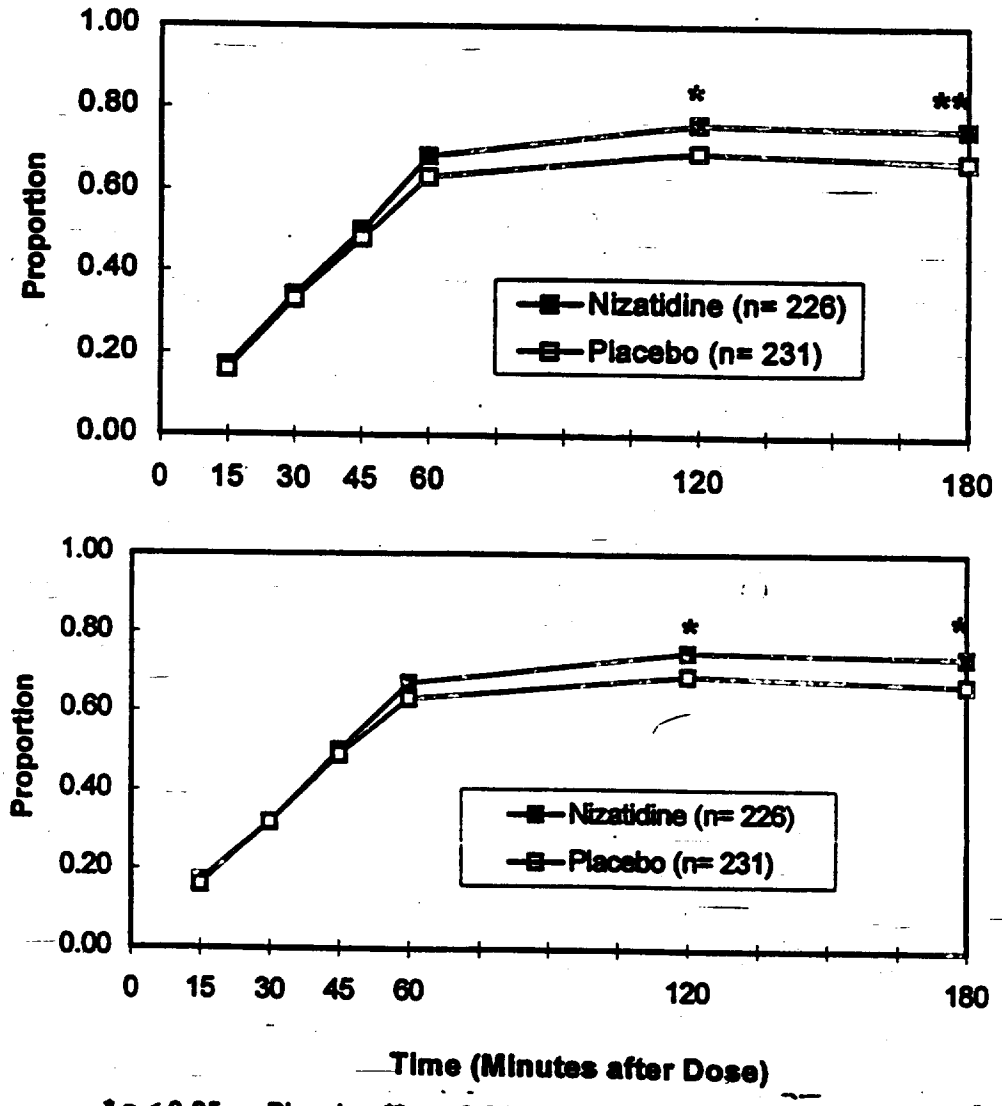

Fig. 2. - Study NZ-95-04: Proportion of Episodes with Adequate Relief at Each Timepoint Based on the First 4 Episodes (Upper Panel) or All Episodes (Lower Panel).